10/789,063 EAST

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	2599	((514/317) or (514/320)).CCLS.	US-PGPUB; USPAT	OR	OFF	2005/12/22 16:17
L2	1715	((546/196) or (546/216)).CCLS.	US-PGPUB; USPAT	OR	OFF	2005/12/22 16:17
L3	3801	L1 or L2	US-PGPUB; USPAT	OR	OFF	2005/12/22 16:17
L4	869	L3 and sulfonyl	US-PGPUB; USPAT	OR	OFF	2005/12/22 16:18
L5	267	L4 and (pyrrolidinone or pyrrolidone)	US-PGPUB; USPAT	OR	OFF	2005/12/22 16:18

10/ 789,063

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspta1202txn

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 09	ACD predicted properties enhanced in REGISTRY/ZREGISTRY
NEWS	4	OCT 03	MATHDI removed from STN
NEWS	5	OCT 04	CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices
NEWS	6	OCT 13	New CAS Information Use Policies Effective October 17, 2005
NEWS	7	OCT 17	STN(R) AnaVist(TM), Version 1.01, allows the export/download of CAplus documents for use in third-party analysis and visualization tools
NEWS	8	OCT 27	Free KWIC format extended in full-text databases
NEWS	9	OCT 27	DIOGENES content streamlined
NEWS	10	OCT 27	EPFULL enhanced with additional content
NEWS	11	NOV 14	CA/CAplus - Expanded coverage of German academic research
NEWS	12	NOV 30	REGISTRY/ZREGISTRY on STN(R) enhanced with experimental spectral property data
NEWS	13	DEC 05	CASREACT(R) - Over 10 million reactions available
NEWS	14	DEC 14	2006 MeSH terms loaded in MEDLINE/LMEDLINE
NEWS	15	DEC 14	2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
NEWS	16	DEC 14	CA/CAplus to be enhanced with updated IPC codes
NEWS	17	DEC 16	MARPATprev will be removed from STN on December 31, 2005
NEWS	18	DEC 21	IPC search and display fields enhanced in CA/CAplus with the IPC reform

NEWS EXPRESS	DECEMBER 02 CURRENT VERSION FOR WINDOWS IS V8.01, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 02 DECEMBER 2005. V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT http://download.cas.org/express/v8.0-Discover/
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

10/ 789,063

* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:42:13 ON 22 DEC 2005

=> file reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 15:42:22 ON 22 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 21 DEC 2005 HIGHEST RN 870514-17-3
DICTIONARY FILE UPDATES: 21 DEC 2005 HIGHEST RN 870514-17-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

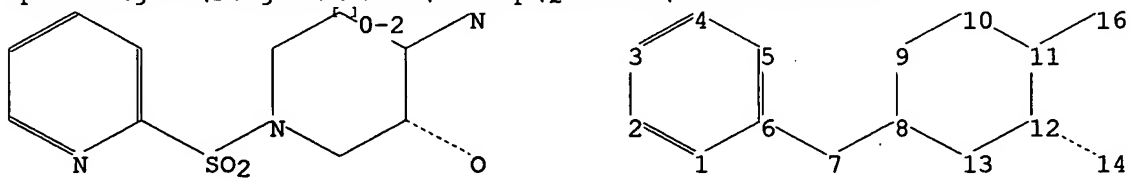
****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=>
Uploading C:\Program Files\Stnexp\Queries\10789063a.str



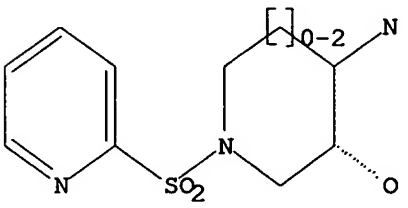
chain nodes :
7 14 16
ring nodes :
1 2 3 4 5 6 8 9 10 11 12 13
chain bonds :

6-7 7-8 11-16 12-14
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 8-9 8-13 9-10 10-11 11-12 12-13
exact/norm bonds :
7-8 11-12 11-16 12-13 12-14
exact bonds :
6-7 8-9 8-13 9-10 10-11
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6
isolated ring systems :
containing 1 : 8 :

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:CLASS 16:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 sample
SAMPLE SEARCH INITIATED 15:42:40 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 49 TO ITERATE

100.0% PROCESSED 49 ITERATIONS 49 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 560 TO 1400
PROJECTED ANSWERS: 560 TO 1400

L2 49 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 15:42:46 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 845 TO ITERATE

100.0% PROCESSED 845 ITERATIONS 827 ANSWERS
SEARCH TIME: 00.00.01

L3 827 SEA SSS FUL L1

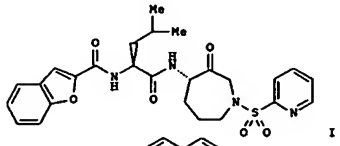
10/ 789,063

```
=> file hcaplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       161.33     161.54

FILE 'HCAPLUS' ENTERED AT 15:42:54 ON 22 DEC 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)
```

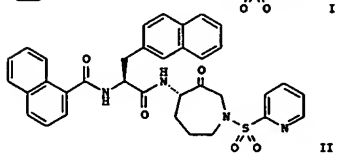


```
FILE COVERS 1907 - 22 Dec 2005  VOL 143 ISS 26
FILE LAST UPDATED: 21 Dec 2005  (20051221/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d his

     (FILE 'HOME' ENTERED AT 15:42:13 ON 22 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 15:42:22 ON 22 DEC 2005
L1             STRUCTURE UPLOADED
L2          49 S L1 SAMPLE
L3         827 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 15:42:54 ON 22 DEC 2005

=> s l3
L4          42 L3

=> d his

     (FILE 'HOME' ENTERED AT 15:42:13 ON 22 DEC 2005)

     FILE 'REGISTRY' ENTERED AT 15:42:22 ON 22 DEC 2005
L1             STRUCTURE UPLOADED
L2          49 S L1 SAMPLE
L3         827 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 15:42:54 ON 22 DEC 2005
L4          42 S L3

=> d l4 1- ibib abs fhitstr
YOU HAVE REQUESTED DATA FROM 42 ANSWERS - CONTINUE? Y/(N):y
```

L4 ANSWER 1 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1059040 HCAPLUS
DOCUMENT NUMBER: 143:460415
TITLE: Azepanone-Based Inhibitors of Human Cathepsin L
AUTHOR(S): Marquis, Robert W.; James, Ian; Zeng, Jin; Trout, Robert E. Lee; Thompson, Scott; Rahman, Attiq; Yamashita, Dennis S.; Xie, Ren; Ru, Yu; Gress, Catherine J.; Blake, Simon; Lark, Michael A.; Hwang, Shing-Mei; Tomaszek, Thaddeus; Offen, Priscilla; Head, Martha S.; Cummings, Maxwell D.; Veber, Daniel F.
CORPORATE SOURCE: Departments of Medicinal Chemistry, Bone and Cartilage Biology Molecular Recognition and Physical and Structural Chemistry, GlaxoSmithKline, Collegeville, PA, 19426, USA
SOURCE: Journal of Medicinal Chemistry (2005), 48(22), 6870-6878
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

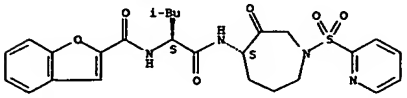


II

AB The extension of a previously-reported cathepsin K azepanone-based inhibitor template to the design and synthesis of potent and selective inhibitors of the homologous cysteine protease cathepsin L is detailed. Structure-activity studies examining the effect of inhibitor selectivity as a function of the P3 and P2 binding elements of the potent cathepsin K inhibitor leucinamide derivative I revealed that incorporation of either a P3 quinoline-8-carboxamide or a naphthalene-1-carboxamide led to increased selectivity for cathepsin L over cathepsin K. Substitution of the P2 leucine of I with either a phenylalanine or a β-naphthylalanine also resulted in an increased selectivity for cathepsin L over cathepsin K. Mol. modeling studies with the inhibitors docked within the active sites of both cathepsins L and K have rationalized the obsd. selectivities. Optimization of cathepsin L binding by the combination of the P3 naphthalene-1-carboxamide with the P2 β-naphthylalanine provided β-naphthylalaninamide deriv. II, which is a potent, selective, and competitive inhibitor of human cathepsin L with a Ki = 0.43 nM.

IT 281217-45-6
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation and structure-activity studies of azepanone-derived inhibitors of cathepsin)
RN 281217-45-6 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:696725 HCAPLUS
DOCUMENT NUMBER: 143:179625
TITLE: Encapsulation of lipid-based formulations in enteric polymers
INVENTOR(S): Pillai, Raviraj S.
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005070401	A1	20050804	WO 2005-US1134	20050113

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

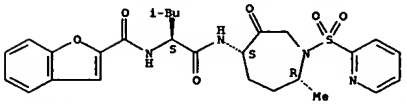
PRIORITY APPLN. INFO.: US 2004-537131P P 20040116

AB A microcapsule comprising a lipid-based core that is encapsulated in an enteric polymer shell providing enhanced bioavailability of a sparingly water-soluble drug as well as modulated release of the drug, wherein the microcapsule is, in one embodiment, prepared by a centrifugal coextrusion process. The lipid-based core comprises lipids carriers, either liquid or solid (m.p. < 100°C), that would provide adequate drug solubilization and is compatible with the enteric shell materials. For example, microcapsules containing a lipidic core comprising a medium chain triglyceride and a sparingly water-soluble drug (SB 462795) and an enteric shell comprising HPMCP-55 were prepared A core contained Labrafac CC 85%, polyglycolized glycerides (Gelucire 44/14) 10%, and SB 462795 5%, and shell contained water 73.0%, NaOH 3.2%, HPMCP-55 22.4%, and glycerin 1.4%. The resulting microcapsule had poor aqueous solubility (< 5 pg/mL). The microcapsules showed negligible drug release in the dissoln. medium at acidic pH and rapid release and drug solubilization in a dissoln. medium that mimics intestinal fluid. The microcapsules can be filled directly into capsule shells or blended with granules containing a different active and then filled into capsule shells suitable for dosing.

IT 362505-84-8, SB 462795
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(encapsulation of lipid-based formulations of sparingly water-soluble drug in enteric polymers)
RN 362505-84-8 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4S,7R)-hexahydro-7-methyl-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 2 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:696636 HCAPLUS
DOCUMENT NUMBER: 143:193920
TITLE: A preparation of derivatives of benzofuran-2-carboxylic acid amide, useful as cysteine protease inhibitors
INVENTOR(S): Clark, William M.; Badham, Neil Francis; Dai, Qunying; Eldridge, Ann Marie; Matsuhashi, Hayao
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005069981	A2	20050804	WO 2005-US2121	20050121

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

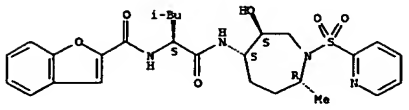
PRIORITY APPLN. INFO.: US 2004-538861P P 20040123
OTHER SOURCE(S): CASREACT 143:193920
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to a preparation of derivs. of benzofuran-2-carboxylic acid amide, useful as cysteine protease inhibitors (no biol. data). For instance, benzofuran derivative I was prepared via amidation of carboxylic acid II by amine III and subsequent oxidation (yield of amidation was 90%).
IT 362507-77-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of derivs. of benzofuran-2-carboxylic acid amide useful as cysteine protease inhibitors)
RN 362507-77-5 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(3S,4S,7R)-hexahydro-3-hydroxy-7-methyl-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 3 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

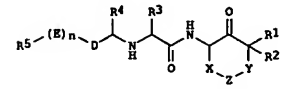


L4 ANSWER 4 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:638869 HCAPLUS
DOCUMENT NUMBER: 143:133700
TITLE: Preparation of peptides as cathepsin cysteine protease inhibitors
INVENTOR(S): Bayly, Christopher; Black, Cameron; Therien, Michel
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

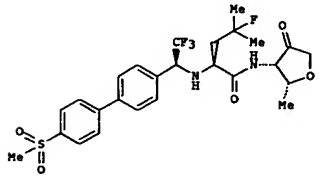
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005066159	A1	20050721	WO 2005-CA7	20050106

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-534920P P 20040108
OTHER SOURCE(S): MARPAT 143:133700
GI



I

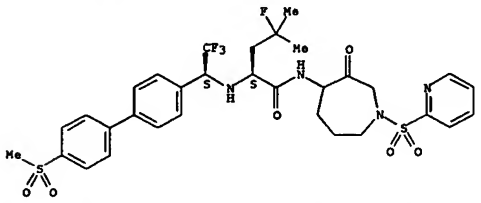


II

AB The invention relates to novel leucinamide derivs. I [X is (CR1R2)0-2; Y, Z are independently CR1R2, O, S, SO2, CO, NH or substituted imino; D, E are independently (un)substituted aryl or heteroaryl; n is 0 or 1; R1, R2 are independently H, halo or (un)substituted alkyl; or CR1R2 is a ring; R3 is alkyl or alkenyl; R4 is haloalkyl; R5 is H, alkyl, alkoxy, aryl, heteroaryl, cycloalkyl, heterocyclyl, OH, acyl, etc.] or their pharmaceutically-acceptable salts or stereoisomers, which are cathepsin cysteine protease inhibitors useful for treating and preventing cathepsin dependent conditions, e.g., osteoporosis, in which inhibition of bone resorption is indicated. Thus, peptide II was prepd. by coupling of N-[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-4-fluoro-L-leucine with (4S,5R)-4-amino-5-methyldihydrofuran-3(2H)-one and [4-(methylthio)phenyl]boronic acid, followed by S-oxidn.
IT 858945-73-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides as cathepsin cysteine protease inhibitors)
RN 858945-73-0 HCAPLUS
CN Pentanamide, 4-fluoro-N-(hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]-4-methyl-2-[[(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]ethyl]amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 4 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



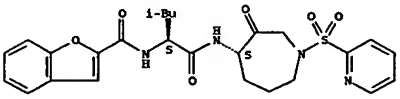
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:303283 HCAPLUS
DOCUMENT NUMBER: 142:367703
TITLE: Methods for diagnosis and treatment of degenerative joint disease by regulating levels of cathepsin K, cathepsin S and tartarate-resistant acid phosphatase in dogs
INVENTOR(S): Muir, Peter; Vanderby, Ray; Provenzano, Paolo Pepe
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 45 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005074800	A1	20050407	US 2004-929919	20040830
CA 2438744	AA	20050228	CA 2003-2438744	20030829
PRIORITY APPLN. INFO.:			US 2003-499105P P	20030829

AB The present invention relates to methods for diagnosis and treatment of degenerative joint disease by regulating levels of cathepsin K, cathepsin S and tartarate-resistant acid phosphatase in dogs. The methods of diagnosis include determining increased expression of enzymes that are upregulated during the progress of joint and ligament inflammation and degeneration. In addition, disclosed are methods of treating the disease including inhibiting the activity of responsible proteases.
IT 281217-45-6, SB-357114
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for diagnosis and treatment of degenerative joint disease by regulating levels of cathepsin K, cathepsin S and tartarate-resistant acid phosphatase in dogs)
RN 281217-45-6 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

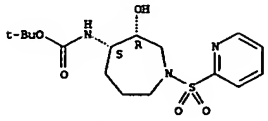
Absolute stereochemistry.



L4 ANSWER 6 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:263672 HCAPLUS
DOCUMENT NUMBER: 142:463586
TITLE: Asymmetric synthesis of a potent azepanone-based inhibitor of the cysteine protease cathepsin K
AUTHOR(S): Lee Trout, Robert E.; Marquis, Robert W.
CORPORATE SOURCE: Department of Medicinal Chemistry, Microbial, Musculoskeletal and Proliferative Diseases, GlaxoSmithKline, Collegeville, PA, 19426, USA
SOURCE: Tetrahedron Letters (2005), 46(16), 2799-2801
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In this account the asym. synthesis of a potent azepanone-based inhibitor of cathepsin K (Ki = 0.16 nM), which was shown to inhibit the production of biomarkers of bone resorption in monkeys was reported. The target compound was N-[(1S)-1-[[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-2-benzofurancarboxamide (SB 357114). The key steps in the synthesis sequence were the utility of the Evans aldol reaction coupled with the ring closing olefin metathesis to assemble the azepanone core contained within SB 357114.
IT 851815-72-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (+)-N-[(S)-[[[(S)-hexa(hydro)(oxo)[(pyridinyl)sulfonyl]-1H-azepin-4-yl]amino]carbonyl][(methyl)butyl]-2-benzofurancarboxamide using Evans aldol reaction and ring closing olefin metathesis as key synthetic steps)
RN 851815-72-0 HCAPLUS
CN Carbamic acid, [(3R,4S)-hexahydro-3-hydroxy-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



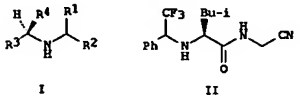
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:219775 HCAPLUS
DOCUMENT NUMBER: 142:280425
TITLE: Preparation of amino acid derivatives as cathepsin inhibitors
INVENTOR(S): Bayly, Christopher; Black, Cameron; McKay, Daniel J.
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005021487	A1	20050310	WO 2004-CA1577	20040823

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-498017P P 20030827
OTHER SOURCE(S): MARPAT 142:280425
GI

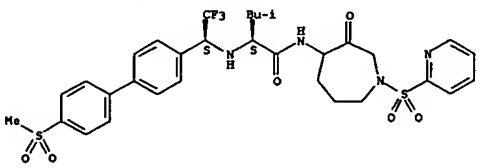


I II

AB The invention relates to compds. I which are cysteine protease inhibitors, including but not limited to inhibitors of cathepsins K, L, S and B, and are useful for treating diseases in which inhibition of bone resorption is indicated, e.g., osteoporosis, osteoarthritis and rheumatoid arthritis. Thus, a mixture of L-leucine Me ester hydrochloride, 2,2,2-trifluoroacetophenone, diisopropylethylamine and TiCl4 in CH2Cl2 was stirred overnight, addnl. TiCl4 added, and the mixture stirred an addnl. 3 h. A solution of NaCNBH3 in MeOH was added and the mixture stirred 2 h to afford Me N-(2,2,2-trifluoro-1-phenylethyl)-L-leucinate. Saponification of the ester and reaction with aminoacetonitrile hydrochloride in DMF in the presence of PyBOP and Et3N yielded L-leucinamide derivative II.
IT 678982-29-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino acid derivs. as cathepsin inhibitors)
RN 678982-29-1 HCAPLUS

L4 ANSWER 7 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
CN Pentanamide, N-[hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]-4-methyl-2-[[(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]ethyl]amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

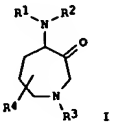


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

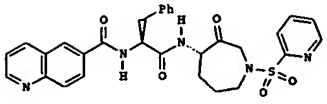
L4 ANSWER 8 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:803931 HCAPLUS
DOCUMENT NUMBER: 141:295878
TITLE: Preparation of aminoazepanones as Cathepsin L inhibitors
INVENTOR(S): Marquis, Robert W.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004192674	A1	20040930	US 2004-772817	20040205
PRIORITY APPLN. INFO.:			US 2003-447558P P	20030214
OTHER SOURCE(S):	MARPAT 141:295878			

GI



I

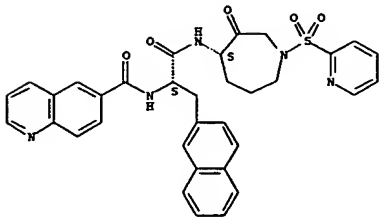


II

AB The title compds. I [R1 = substituted aminoalkylcarbonyl; R2 = H, alkyl, arylalkyl, etc.; R3 = H, alkyl, cycloalkyl, arylalkyl, etc.; R4 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts are prepared and disclosed as inhibitors of Cathepsin L. Thus, e.g., II was prepared in a multistep synthesis employing N-Boc-phenylalanine. Consequently they are useful for preventing or treating diseases in which cathepsin L is implicated, such as rheumatoid arthritis or inhibition of pos. selection of CD4 + T-cells by cortical thymic epithelial cells.
IT 350796-38-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

L4 ANSWER 8 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(drug candidate; prepn. of aminoazepanones as inhibitors of Cathepsin L)
RN 350796-38-2 HCAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

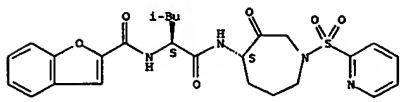


L4 ANSWER 9 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:565073 HCAPLUS
DOCUMENT NUMBER: 141:117186
TITLE: Use of cathepsin k inhibitors for the treatment of glaucoma
INVENTOR(S): Shepard, Allan; Clark, Abbot F.; Jacobson, Nasreen
PATENT ASSIGNEE(S): Alcon, Inc., Switz.
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058238	A1	20040715	WO 2003-US40511	20031219
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 2002-436126P P	20021223

AB Compns. containing inhibitors of cathepsin K (CTSK) expression and/or activity are provided. Methods for the treatment of glaucoma using the compns. of the invention are further provided. The cathepsin K antagonist is selected from, but not limited to, the group consisting of monensin, brefeldin A, tunicamycin and 1,3-bis(acylamino)-2-propanone derivs., cycloaltilisin 6, cycloaltilisin 7, AC-3-1, AC-3-3, AC-5-1, haploscleridamine, SB-331750, SB-357114, peptidomimetic aminomethyl ketones, α,α'-diacylamino ketones, alkoxymethyl ketones, cyanamides, pyridoxal propionate derivs. (including Clik-164 and Clik-166), SB-290190, α-alkoxy ketone derivs., cyanamide derivs., and Nα-acyl-α-amino acid-(arylaminoethyl)amides.
IT 281217-45-6, SB-357114
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of cathepsin k inhibitors for treatment of glaucoma)
RN 281217-45-6 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 9 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L4 ANSWER 10 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

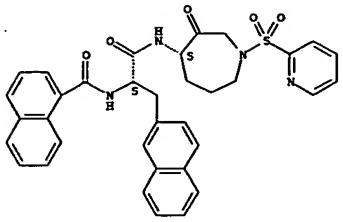
ACCESSION NUMBER: 2004:500870 HCAPLUS
DOCUMENT NUMBER: 142:16826
TITLE: Medicine for treating obesity, diabetes mellitus and related diseases
INVENTOR(S): Chen, Jingming; Yong, Heng
PATENT ASSIGNEE(S): Shen, Aifu, Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 62 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1400018	A	20030305	CN 2001-123953	20010808
PRIORITY APPLN. INFO.:			CN 2001-123953	20010808

AB The application of the inhibitors of cathepsins L, K, and S for treating obesity, diabetes mellitus, and their related diseases (such as hyperinsulina, hyperglycemia, hypertension, heart diseases, infecundity, etc.) is presented. The inhibitors of cathepsins L, K, and S are antisense sequence of human cathepsin L cDNA or its un-translated region at 5' end, anti-cathepsin L antibody, cystatin C mutant, saxiphilin, precursor of cathepsin L, epoxysuccinate derivative lowering the activity of cathepsin L, aziridine-2,3-dicarboxylate derivative or peptide aldehyde derivative
inhibiting the activity of cathepsin L, or dipeptide hydroxy-amidic acid ester derivative or sulfonyl derivative inhibiting the activity of cathepsin L.
IT 350796-39-3P
RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(medicine for treating obesity diabetes mellitus and related diseases)
RN 350796-39-3 HCAPLUS
CN 2-Naphthalenepropanamide, N-[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]-α-[(1-naphthalenylcarbonyl)amino]-, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 10 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



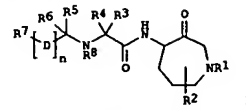
L4 ANSWER 11 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:333709 HCAPLUS
DOCUMENT NUMBER: 140:321727
TITLE: Preparation of 4-aminoazepan-3-one peptides as cathepsin K inhibitors useful in the treatment of osteoporosis
INVENTOR(S): Black, Cameron
PATENT ASSIGNEE(S): Merck Frosst Canada & Co., Can.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

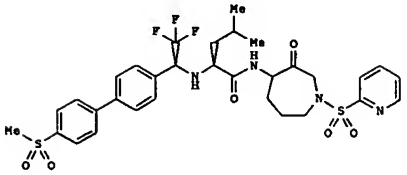
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004033445	A1	20040422	WO 2003-CA1551	20031007
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2500317	AA	20040422	CA 2003-2500317	20031007
EP 1551823	A1	20050713	EP 2003-757604	20031007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2002-416892P	P 20021008
			WO 2003-CA1551	W 20031007

OTHER SOURCE(S): MARPAT 140:321727
GI

L4 ANSWER 11 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I

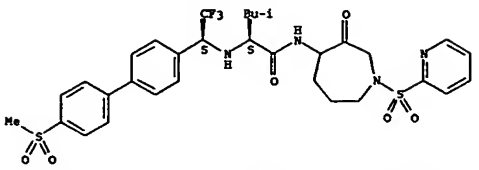


II

AB The invention relates to azepinones I [R1 is H, alkyl, a sulfonyl or acyl group, arylalkyl; R2 is H or (cyclo)alkyl; R3 is H, alk(en)yl, haloalk(en)yl or cycloalk(en)yl; or R3R4C is (un)substituted (hetero)cycloalk(en)yl; R5 is H, alkyl or haloalkyl; R6 is haloalkyl, (un)substituted (hetero)aryl or (hetero)arylalkyl; R7 is H, alk(en)(yn)yl, alkoxy, halo, nitro, cyano, (hetero)aryl, carboxy, etc.; D is (un)substituted alk(en)ylene or (hetero)arylene; n is 0-3] or their pharmaceutically-acceptable salts, stereoisomers and N-oxides which are cysteine protease inhibitors, in particular, inhibitors of cathepsins K, L, S and B. These compds. are useful for treating diseases, e.g., osteoporosis, in which inhibition of bone resorption is indicated. Thus, aminoazepanone peptide II was prepared by a multistep procedure starting with reaction of silyl-protected L-leucinol with trifluoroacetaldehyde Me hemiacetal.
IT 678982-29-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoazepanone peptides as cathepsin K inhibitors for treatment of osteoporosis)
RN 678982-29-1 HCAPLUS
CN Pentanamide, N-[hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]-4-methyl-2-[[(1S)-2,2,2-trifluoro-1-[4'-(methylsulfonyl)[1,1'-biphenyl]-4-yl]ethyl]amino]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 11 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



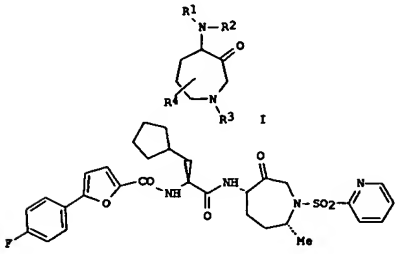
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:182661 HCAPLUS
DOCUMENT NUMBER: 140:235616
TITLE: Preparation of 4-amino-azepan-3-ones as cathepsin S inhibitors
INVENTOR(S): Bondinell, William E.; Hall, Ralph F.; Jin, Qi; Kerns, Jeffrey K.; Nie, Hong; Widdowson, Katherine L.
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004017911	A2	20040304	WO 2003-US26358	20030822
WO 2004017911	A3	20040701		
W: AE, AG, AL, AU, BA, BB, BR, BZ, CA, CN, CO, CR, CU, DM, DZ, EC, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, OM, PH, PL, RO, SC, SG, TN, TT, UA, US, UZ, VN, YU, ZA				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1539178	A2	20050615	EP 2003-751880	20030822
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-405227P P 20020822
WO 2003-US26358 W 20030822
OTHER SOURCE(S): MARPAT 140:235616
GI



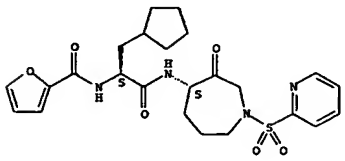
L4 ANSWER 12 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

AB 4-Amino-azepan-3-ones of formula I [R1 = (substituted) aminomethylcarbonyl, acyl, etc.; R2 = H, alkyl, arylalkyl, etc.; R3 = H, alkyl, cycloalkyl-alkyl, acyl, etc.; R4 = alkyl, etc.] are prepared The compds. are useful as protease inhibitors, particularly of cathepsin S, and as such are useful for preventing a number of diseases amongst which are atherosclerotic lesions and pulmonary diseases such as asthma and allergic reactions (no data). Thus, II was prepared from 4-fluorophenylboronic acid and 5-bromofuran-2-carboxylic acid [(S)-2-cyclopentyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridin-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl]-amide (preparation given) in 24% yield.

IT **666725-67-3P**
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino-azepanones as cathepsin S inhibitors)

RN 666725-67-3 HCAPLUS
CN 2-Furancarboxamide, N-[(1S)-1-(cyclopentylmethyl)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 13 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:142902 HCAPLUS
DOCUMENT NUMBER: 140:187404
TITLE: Electrospun amorphous pharmaceutical compositions
INVENTOR(S): Ignatious, Francis; Sun, Linghong
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004014304	A2	20040219	WO 2003-US24641	20030807
WO 2004014304	A3	20040624		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2494865	AA	20040219	CA 2003-2494865	20030807
EP 1534250	A2	20050601	EP 2003-784959	20030807
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003013222	A	20050614	BR 2003-13222	20030807
JP 2005534716	T2	20051117	JP 2004-527797	20030807
NO 2005001123	A	20050506	NO 2005-1123	20050302

PRIORITY APPLN. INFO.: US 2002-401726P P 20020807
WO 2003-US24641 W 20030807

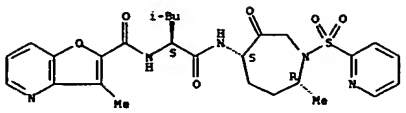
AB The present invention is directed to use of electrospinning, i.e. the process of making polymer nanofibers from either a solution or melt under elec. forces, to prepare stable, solid dispersions of amorphous drugs in polymer nanofibers. Thus, carvedilol-HBr monohydrate wa dissolved in THF and water. The solution was added to Polyox WSR1105 in MeCN solution This solution was spun to give nanofibers, and the morphol. of the drug was shown to be amorphous.

IT **362505-94-0**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(electrospun amorphous pharmaceutical compns.)

RN 362505-94-0 HCAPLUS
CN Furo[3,2-b]pyridine-2-carboxamide, N-[(1S)-1-[[[(4S,7R)-hexahydro-7-methyl-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-3-methyl- (9CI) (CA INDEX NAME)

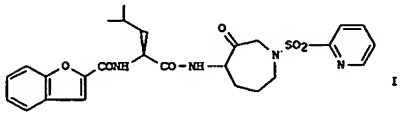
Absolute stereochemistry.

L4 ANSWER 13 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

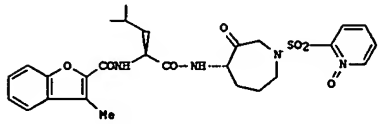


L4 ANSWER 14 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:921964 HCAPLUS
DOCUMENT NUMBER: 140:280693
TITLE: An Azepanone-Based Inhibitor of Human Cathepsin K with Improved Oral Bioavailability in the Rat and the Monkey
AUTHOR(S): Marquis, Robert W.; Ward, Keith W.; Roethke, Theresa; Smith, Brian R.; Ru, Yu; Yamashita, Dennis S.; Tomaszek, Thaddeus A.; Gorycki, Peter D.; Cheng, H.-Y.; James, Ian E.; Stroup, George B.; Lark, Michael W.; Gowen, Maxine; Veber, Daniel F.
CORPORATE SOURCE: Departments of Medicinal Chemistry, Drug Metabolism and Pharmacokinetics, Mechanistic Enzymology Computational Analytical and Structural Sciences and Bone and Cartilage Biology, GlaxoSmithKline, Collegeville, PA, 19426, USA
SOURCE: Molecular Pharmaceutics (2004), 1(1), 97-100 CODEN: MPOHBP; ISSN: 1543-8384
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

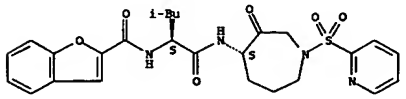


II

AB Pharmacokinetic evaluation of the potent azepanone-based cathepsin K inhibitor 3 (I) showed that it has an oral bioavailability of 42% in the rat and 4.8% in the monkey. The less than optimal oral bioavailabilities of 3 in the rat and the monkey precluded this analog from being subjected to more detailed pharmacokinetic and pharmacodynamic analyses. In vitro and in vivo studies aimed at identifying the mechanisms which may be limiting the bioavailability of 3 in these species served to guide the syntheses of subsequent analogs for further evaluation. These studies have led to the identification of azepanone 6 (II) that possesses improved oral bioavailability in both the rat (66.3%) and the monkey (23.4%).
IT 281217-45-6

L4 ANSWER 14 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
RL: PKT (Pharmacokinetics); PRP (Properties); BIOL (Biological study)
(azepanone-based inhibitor of human cathepsin K with improved oral bioavailability in rat and the monkey)
RN 281217-45-6 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

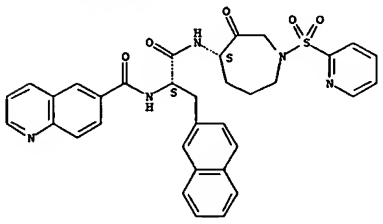


REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:665404 HCAPLUS
DOCUMENT NUMBER: 141:103796
TITLE: Potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro. [Erratum to document cited in CA135:120165]
AUTHOR(S): James, Ian E.; Marquis, Robert W.; Blake, Simon M.; Hwang, Shing Mei; Gress, Catherine J.; Ru, Yu; Zembryki, Denise; Yamashita, Dennis S.; McQueney, Michael S.; Tomaszek, Thaddeus A.; Oh, Hye-Ja; Gowen, Maxine; Veber, Daniel F.; Lark, Michael W.
CORPORATE SOURCE: Departments of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Journal of Biological Chemistry (2003), 278(34), 32484 CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In Tables I and II, analogs SB-468430 and SB-468433 were originally reported to contain the quinoline-8-carboxamide moiety. Subsequent resynthesis revealed that in actuality these analogs contain the isomeric quinoline-6-carboxamide moiety. The modified structures are given in revised Tables I and II. Corrected Ki values for cathepsin L and cathepsin K in Table I are also given.
IT 350796-38-2, SB 468430
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro (Erratum))
RN 350796-38-2 HCAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 16 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:590812 HCAPLUS
DOCUMENT NUMBER: 139:133836
TITLE: Preparation of 4-aminoazepan-3-ones as protease inhibitors
INVENTOR(S): Marquis, Robert Wells; Ru, Yu; Veber, Daniel Frank; Cummings, Maxwell David; Thompson, Scott Kevin; Yamashita, Dennis Shinji
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 126 pp., Cont.-in-part of U.S. Ser. No. 593,845, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

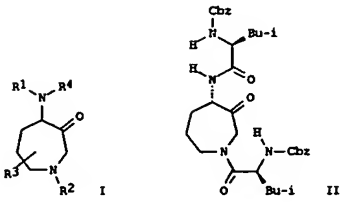
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003144175	A1	20030731	US 2001-881334	20010614
WO 2000038687	A1	20000706	WO 1999-US30730	19991221
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1384713	A1	20040128	EP 2003-76211	19991221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY				
ZA 2001004208	A	20020523	ZA 2001-4208	20010523
WO 2002017924	A1	20020307	WO 2001-US27178	20010831
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001086983	A5	20020313	AU 2001-86983	20010831
EP 1320370	A1	20030625	EP 2001-966474	20010831
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004509083	T2	20040325	JP 2002-522897	20010831
US 2004002487	A1	20040101	US 2003-404716	20030401
US 2005256104	A1	20051117	US 2005-152745	20050614

PRIORITY APPLN. INFO.:

US 1998-113636P	P	19981223
US 1999-164581P	P	19991110
WO 1999-US30730	A2	19991221
US 2000-593845	B2	20000614
EP 1999-963112	A3	19991221
US 2000-653815	A2	20000901
US 2001-881334	A2	20010614
WO 2001-US27178	W	20010831

L4 ANSWER 16 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
US 2003-404716 B1 20030401

OTHER SOURCE(S): MARPAT 139:133836
GI



I II

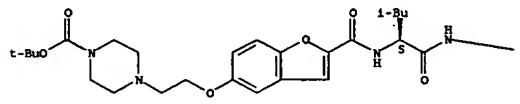
AB Aminoazepanones I [R1 = alkanoyl, amino-, alkoxy-, or alkylthioalkanoyl, etc.; R2 = H, alkyl, cycloalkyl, cycloalkylalkyl, (thio)acyl, alkylsulfonyl, etc.; R3 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, etc.; R4 = H, alkyl, arylalkyl, etc.] or their pharmaceutically-acceptable salts were prepared as protease inhibitors, including cathepsin K, for treating diseases of excessive bone loss or cartilage or matrix degradation, gingival disease, arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Thus, compound II (Cbz = benzyloxycarbonyl) was prepared by a multistep procedure.

IT 281214-88-8P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of (acylamino)azepanones as protease inhibitors)

RN 281214-88-8 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[2-[[2-[[[(1S)-1-[[[hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]amino]carbonyl]-5-benzofuranyl]oxy]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

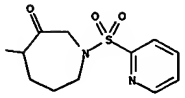
Absolute stereochemistry.

PAGE 1-A



L4 ANSWER 16 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-B



L4 ANSWER 17 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:511076 HCAPLUS
DOCUMENT NUMBER: 139:85252
TITLE: Preparation of aminoazepinones as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Veber, Daniel F.; Yamashita, Dennis S.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053331	A2	20030703	WO 2001-US51647	20011119
WO 2003053331	A3	20031113		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2436850	AA	20030703	CA 2001-2436850	20011119
EP 1392657	A2	20040303	EP 2001-275089	20011119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001015473	A	20040928	BR 2001-15473	20011119
JP 2005513083	T2	20050512	JP 2003-554091	20011119
ZA 2003003848	A	20040628	ZA 2003-3848	20030516

PRIORITY APPLN. INFO.:

US 2000-252508P	P	20001122
WO 2001-US51647	W	20011119

OTHER SOURCE(S): CASREACT 139:85252; MARPAT 139:85252
GI

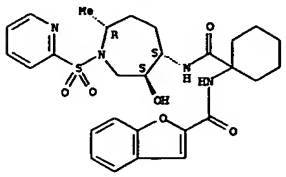
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. I [R1 = (un)substituted aminocycloalkylmethylcarbonyl; R2 = H, alkyl, arylalkyl, and heteroalkyl; R3 = H, alkyl, cycloalkylalkyl, arylalkyl, and heteroalkyl; R4 = H, alkyl, cycloalkylalkyl, heteroalkyl, alkylketone, etc.] and pharmaceutically acceptable salts, hydrates and solvates thereof are prepared and claimed as inhibitors or proteases, including cathepsin K. Thus, II was prepared in eleven steps as the racemate and resolved via HPLC. Compds. of the invention were selective to inhibition of cathepsin K vs. L, S and B, e.g., II possessed Ki of 1.4 nM for inhibition of human cathepsin K vs. 239, 390 and 926 nM for L, S and B, resp. As protease inhibitors, I are claimed for treatment of diseases of excessive bone loss or cartilage or matrix degradation

IT 362508-49-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(claimed intermediate; preparation and protease inhibitory activity of azepinones)

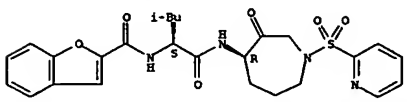
L4 ANSWER 17 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
RN 362508-49-4 HCAPLUS
CN 2-Benzofurancarboxamide, N-[1-[[[(3S,4S,7R)-hexahydro-3-hydroxy-7-methyl-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]cyclohexyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 18 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:509414 HCAPLUS
DOCUMENT NUMBER: 140:52478
TITLE: The role of conformational constraint in improved oral bioavailability of cathepsin K inhibitors
AUTHOR(S): Veber, Daniel F.; Marquis, Robert W.; Yamashita, Dennis S.; Ru, Yu; Oh, Hye-Ja; Ward, Keith W.; Smith, Brian R.
CORPORATE SOURCE: SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Peptides 2000, Proceedings of the European Peptide Symposium, 26th, Montpellier, France, Sept. 10-15, 2000 (2001), Meeting Date 2000, 113-114. Editor(s): Martinez, Jean; Fehrentz, Jean-Alain. Editions EDK: Paris, Fr.
CODEN: 69KDWK; ISBN: 2-84254-048-4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. We have been engaged in efforts to discover inhibitors of the osteoclast derived cysteine protease, cathepsin K, for use as a bone anti-resorptive to suppress the bone loss characteristic of diseases such as osteoporosis and rheumatoid arthritis. Potent and reversible inhibitors of cathepsin K have been designed but their development as drugs has been limited by poor oral bioavailability and rapid clearance from circulation. This article identifies some cyclic 5 and 6 member ring structures discovered in the course of trying to improve oral bioavailability of ketone-based cathepsin K inhibitors.
IT 281214-75-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of conformational constraint in improved oral bioavailability of cathepsin K inhibitors)
RN 281214-75-3 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:434525 HCAPLUS
DOCUMENT NUMBER: 139:22118
TITLE: Methods and intermediates for the synthesis of azepines
INVENTOR(S): Conde, Jose J.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045909	A2	20030605	WO 2002-US37423	20021120
WO 2003045909	A3	20031211		

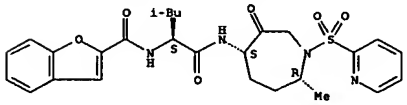
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-331949P P 20011121
OTHER SOURCE(S): CASREACT 139:22118; MARPAT 139:22118
GI

AB Azepines I [R alkyl, aryl, acyl, thioacyl; R1 = alkyl] were prepared by cyclizing O2NCH2CHR2CHR3CHR4NRCH2CHO [at least two of R2-R4 = H, the other = alkyl]. Thus, CH2:CHCOMe was treated with MeNO2 to give O2N(CH2)3COMe which was treated with PhCH2NHCH2CO2Et and resolved to give (R)-O2N(CH2)3CHMeN(CH2Ph)CH2CO2Et. This ester was reduced to (R)-O2N(CH2)3CHMeN(CH2Ph)CH2CHO and cyclized over Amberlyst A-21 to give the azepine II [R5 = NO2]. The NO2 group was reduced and acylated with Boc-Leu-OH to give II [R5 = Boc-Leu-NH].
IT 362505-84-8P
RL: PNU (Preparation, unclassified); PREP (Preparation)
(methods and intermediates for synthesis of azepines)
RN 362505-84-8 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4S,7R)-hexahydro-7-methyl-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 19 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

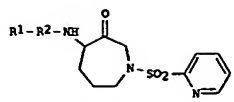


L4 ANSWER 20 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:888706 HCAPLUS
DOCUMENT NUMBER: 137:370363
TITLE: Preparation of 4-amino-azepan-3-one derivatives as protease inhibitors
INVENTOR(S): Xie, Ren; Yamashita, Dennis S.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

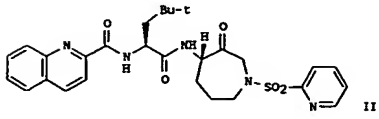
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092563	A2	20021121	WO 2002-US15376	20020515
WO 2002092563	A3	20030403		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1401453	A2	20040331	EP 2002-744152	20020515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004527575	T2	20040909	JP 2002-589449	20020515
US 2004157828	A1	20040812	US 2003-478619	20031117
PRIORITY APPLN. INFO.:			US 2001-291545P P	20010517
			US 2001-292646P P	20010522
			WO 2002-US15376 W	20020515

OTHER SOURCE(S): MARPAT 137:370363
GI

L4 ANSWER 20 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I



II

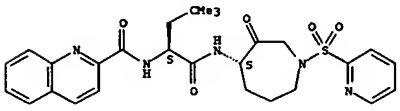
AB 4-Aminoazepan-3-one derivs. of formula I [R1 = 3-methylbenzofuran-2-carbonyl, benzofuran-2-carbonyl, 5-methoxybenzofuran-2-carbonyl, benzothiophene-2-carbonyl, quinoline-2-carbonyl, quinoline-3-carbonyl, thiophene-2-carbonyl, thiophene-3-carbonyl, 5-methylthiophene-2-carbonyl, furan-2-carbonyl, furan-3-carbonyl, thieno[3,2-b]thiophene-2-carbonyl; R2 = L-tert-butylalaninyl, L-2-thiophenylalaninyl, L-cyclohexylglycinyl, L-allo-isoleucinyl, tetrahydroisoquinoline-3-carbonyl, L-prolinyl, (S)-2-amino-4-methanesulfonylbutanoyl, (S)-piperidine-2-carbonyl] are prepared which inhibit proteases, including cathepsin K. The compds. are useful for treating diseases of excessive bone loss or cartilage or matrix degradation, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Thus, II was prepared from 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester hydrochloride, 2-pyridinesulfonyl chloride, Boc-L-tert-butylalanine and quinaldic acid. The prepared compds. had Ki values between 2 nM and 1000 nM against cathepsin K in inhibition assays.

IT 475285-72-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoazepanone derivs. as protease inhibitors)

RN 475285-72-4 HCAPLUS
CN 2-Quinolinecarboxamide, N-[(1S)-1-[[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3,3-dimethylbutyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

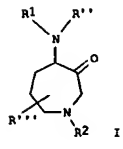
L4 ANSWER 20 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



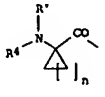
L4 ANSWER 21 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:171694 HCAPLUS
DOCUMENT NUMBER: 136:232208
TITLE: Preparation of 4-aminoazepan-3-one parasitic cysteine protease inhibitors effective against malaria and other diseases
INVENTOR(S): Tew, David G.; Thompson, Scott K.; Veber, Daniel F.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, UK
SOURCE: PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002017924	A1	20020307	WO 2001-US27178	20010831
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003144175	A1	20030731	US 2001-881334	20010614
AU 2001086983	A5	20020313	AU 2001-86983	20010831
EP 1320370	A1	20030625	EP 2001-966474	20010831
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004509083	T2	20040325	JP 2002-522897	20010831
PRIORITY APPLN. INFO.:			US 2000-653815	A2 20000901
			US 2001-881334	A2 20010614
			US 1998-113636P	P 19981223
			US 1999-164581P	P 19991110
			WO 1999-US30730	A2 19991221
			US 2000-593845	B2 20000614
			WO 2001-US27178	W 20010831

OTHER SOURCE(S): MARPAT 136:232208
GI



I



II

AB The present invention relates to methods of treating parasitic diseases which are mediated by cysteine proteases by administration of

L4 ANSWER 21 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

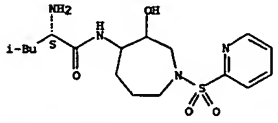
4-aminoazepan-3-one protease inhibitors I (e.g. benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-oxoazepan-4-ylcarbamoyl)-3-methylbutyl]amide) and pharmaceutically acceptable salts, hydrates and solvates thereof. In particular, the present invention relates to a method of treating malaria by inhibiting the cysteine protease falcipain. Other diseases against which the claimed compds. are effective include trypanosomiasis (African sleeping sickness, Chagas disease), leishmaniasis, schistosomiasis, onchocerciasis (river blindness) and giardiasis. In I: R1 is R4NR'CHR3C(O)-, R5XCHR3C(O)-, R3CH2C(O)-, R4NR'CR''''R3C(O)-, II. R2 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R9C(O)-, R9C(S)-, R9SO2-, R9OC(O)-, R9R11NC(O)-, R9R11NC(S)-, R9(R11)NSO2-, 3-(2-pyridyl)benzylcarbonyl, 2-(3-(2-pyridyl)phenyl)ethyl, R7NR6CHR8Z-, and R9SO2R11NC(O)-. R3 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. R3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring. R4 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R5C(O)-, R5C(S)-, R5SO2-, R5OC(O)-, R5R12NC(O)-, and R5R12NC(S)-. R5 is H, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl and Het-C0-6alkyl. R6 is H, C1-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl. R7 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R10C(O)-, R10C(S)-, R10SO2-, R10OC(O)-, R10R13NC(O)-, and R10R13NC(S)-. R8 is H, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. R9, R10 independently = C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl and Het-C0-6alkyl. R11, R12, R13, R', R'' independently = H, C1-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl. R''' is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl; R'''' is C1-6alkyl, C3-6cycloalkyl-C0-6alkyl C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. X is CH2, S, and O; Z is C(O) and CH2; n is 1-5. Although the methods of prepn. are not claimed, 220 example prepns. are included.

IT **281219-75-8P**, (S)-2-Amino-4-methylpentanoic acid [3-hydroxy-1-(pyridine-2-sulfonyl)azepan-4-yl]amide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of 4-aminoazepan-3-one parasitic cysteine protease inhibitors effective against malaria and other diseases)

RN 281219-75-8 HCAPLUS

CN Pentanamide, 2-amino-N-[hexahydro-3-hydroxy-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]-4-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN

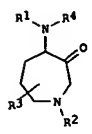
ACCESSION NUMBER: 2001:923616 HCAPLUS
DOCUMENT NUMBER: 136:53691
TITLE: Preparation of 4-amino-azepan-3-one protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Ru, Yu; Veber, Daniel F.; Cummings, Maxwell D.; Thompson, Scott K.; Yamashita, Dennis
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 322 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001095911	A1	20011220	WO 2001-US19062	20010614
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2412353	AA	20011220	CA 2001-2412353	20010614
EP 1307204	A1	20030507	EP 2001-946344	20010614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004503502	T2	20040205	JP 2002-510089	20010614
BR 2001011693	A	20040406	BR 2001-11693	20010614
NZ 522965	A	20040625	NZ 2001-522965	20010614
BG 107327	A	20030731	BG 2002-107327	20021128
NO 2002005786	A	20030212	NO 2002-5786	20021202
ZA 2002009808	A	20040709	ZA 2002-9808	20021203

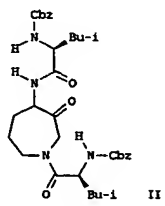
PRIORITY APPLN. INFO.: US 2000-593845 A2 20000614
WO 2001-US19062 W 20010614

OTHER SOURCE(S): MARPAT 136:53691

GI



I



II

L4 ANSWER 21 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

L4 ANSWER 22 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

AB The title compds. [I; R1 = COCR13NR11R12, COCR13XR15, COCH2R13; R2 = H, alkyl, cycloalkylalkyl, etc.; R3 = H, alkyl, cycloalkylalkyl, etc.; R4 = H, alkyl, arylalkyl, etc.; R11 = H, alkyl, arylalkyl, etc.; R12 = H, alkyl, cycloalkyl, etc.; R13 = H, alkyl, alkenyl, etc.; R15 = H, alkyl, alkenyl, etc.] which inhibit proteases (no data), including cathepsin K, and are useful for treating diseases of excessive bone loss or cartilage or matrix degradation including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease, were prepared E.g., a multi-step synthesis of compound II was given.

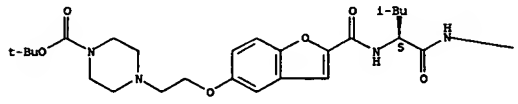
IT **281214-88-8P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 4-amino-azepan-3-one protease inhibitors)

RN 281214-88-8 HCAPLUS

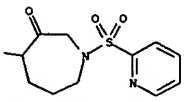
CN 1-Piperazinecarboxylic acid, 4-[2-[[2-[[[(1S)-1-[[[hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]amino]carbonyl]-5-benzofuranyl]oxy]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



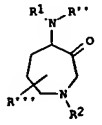
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:868156 HCAPLUS
DOCUMENT NUMBER: 136:6349
TITLE: Preparation of 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Cummings, Maxwell D.; Marquis, Robert W., Jr.; Ru, Yu; Thompson, Scott K.; Veber, Daniel F.; Yamashita, Dennis S.
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001089451	A2	20011129	WO 2001-US12326	20010417
WO 2001089451	A3	20020404		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2406829	AA	20011129	CA 2001-2406829	20010417
AU 2001090507	A5	20011203	AU 2001-90507	20010417
EP 1278502	A2	20030129	EP 2001-970508	20010417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004526662	T2	20040902	JP 2001-585697	20010417
ZA 2002007872	A	20050606	ZA 2002-7872	20021001
NO 2002005005	A	20021206	NO 2002-5005	20021017
US 2003114437	A1	20030619	US 2002-258053	20021017
US 2004229863	A1	20041118	US 2004-797828	20040310

PRIORITY APPLN. INFO.:
US 2000-198493P P 20000418
US 2001-273811P P 20010307
WO 2001-US12326 W 20010417
US 2002-258053 B1 20021017

OTHER SOURCE(S): MARPAT 136:6349
GI

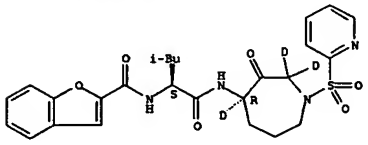


I

L4 ANSWER 23 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

AB 4-Aminoazepan-3-one derivs. I [R1 is an acyl group R3CH2CO, R4NR'CHR3CO or R5-X-CHR3CO; R2-R5 = H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, etc.; R', R'' = H, alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; X = CH2, S or O; R''' = cycloalkyl, cycloalkyl or any group given for R' and R''; R3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring] or their pharmaceutically acceptable salts were prepared as protease inhibitors, particularly cathepsin S, for treating various diseases. Thus, benzofuran-2-carboxylic acid [(S)-2-cyclohexyl-1-[3-oxo-1-(pyridine-2-sulfonyl)azepan-4-ylcarbamoyl]ethyl]amide was prepared by a multistep procedure involving coupling of 4-amino-1-(pyridine-2-sulfonyl)azepan-3-ol (preparation given) with N-Boc-cyclohexylalanine (Boc = tert-butoxycarbonyl), deprotection, coupling with benzofuran-2-carboxylic acid, and oxidation with Dess-Martin reagent.
IT 281216-44-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aminoazepanone cyclohexylalanine derivs. as protease inhibitors)
RN 281216-44-2 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-2,4-d2-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl-2-d]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 24 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:780691 HCAPLUS
DOCUMENT NUMBER: 135:327371
TITLE: 4-Amino-azepan-3-one inhibitors of cathepsin L, their preparation, and their therapeutic use
INVENTOR(S): Cummings, Maxwell D.; Marquis, Robert W., Jr.; Ru, Yu; Thompson, Scott K.; Veber, Daniel F.; Yamashita, Dennis S.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

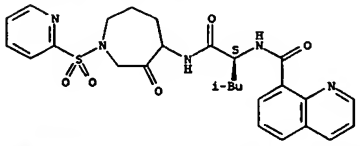
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001078734	A1	20011025	WO 2001-US12386	20010417
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1303281	A1	20030423	EP 2001-927076	20010417
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003531122	T2	20031021	JP 2001-576034	20010417
US 2004034013	A1	20040219	US 2002-258412	20021017

PRIORITY APPLN. INFO.:
US 2000-197717P P 20000418
WO 2001-US12386 W 20010417

OTHER SOURCE(S): MARPAT 135:327371
AB Methods are provided which use 4-amino-azepan-3-one protease inhibitors of cathepsin L in the treatment of diseases in which cathepsin L is implicated, especially treatment or prevention of rheumatoid arthritis; cancer metastasis; diseases requiring inhibition of tissue destruction by macrophages, particularly lung macrophages, such as asthma, chronic obstructive pulmonary disease (COPD), and emphysema; and diseases requiring, for therapy, inhibition of pos. selection of CD4+T- cells by cortical thymic epithelial cells.
IT 281215-01-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(aminoazepanone inhibitors of cathepsin L, preparation, and therapeutic use)
RN 281215-01-8 HCAPLUS
CN 8-Quinolinecarboxamide, N-[(1S)-1-[[[hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 24 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



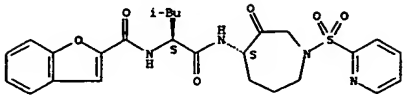
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 25 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:746949 HCAPLUS
DOCUMENT NUMBER: 136:395726
TITLE: Potent and selective inhibition of human cathepsin K leads to inhibition of bone resorption in vivo in a nonhuman primate
AUTHOR(S): Stroup, George B.; Lark, Michael W.; Veber, Daniel F.; Bhattacharyya, Amit; Blake, Simon; Dare, Lauren C.; Erhard, Karl F.; Hoffman, Sandra J.; James, Ian E.; Marquis, Robert W.; Ru, Yu; Vasko-Moser, Janice A.; Smith, Brian R.; Tomaszek, Thadeus; Gowen, Maxine
CORPORATE SOURCE: Department of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA
SOURCE: Journal of Bone and Mineral Research (2001), 16(10), 1739-1746
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cathepsin K is a cysteine protease that plays an essential role in osteoclast-mediated degradation of the organic matrix of bone. Knockout of the enzyme in mice, as well as lack of functional enzyme in the human condition pycnodysostosis, results in osteopetrosis. These results suggests that inhibition of the human enzyme may provide protection from bone loss in states of elevated bone turnover, such as postmenopausal osteoporosis. To test this theory, we have produced a small mol. inhibitor of human cathepsin K, SB-357114, that potently and selectively inhibits this enzyme (Ki = 0.16 nM). This compound potently inhibited cathepsin activity in situ, in human osteoclasts (inhibitor concentration [IC]50 = 70 nM) as well as bone resorption mediated by human osteoclasts in vitro (IC50 = 29 nM). Using SB-357114, we evaluated the effect of inhibition of cathepsin K on bone resorption in vivo using a nonhuman primate model of postmenopausal bone loss in which the active form of cathepsin K is identical to the human orthologue. A gonadotropin-releasing hormone agonist (GnRHa) was used to render cynomolgus monkeys estrogen deficient, which led to an increase in bone turnover. Treatment with SB-357114 (12 mg/kg s.c.) resulted in a significant reduction in serum markers of bone resorption relative to untreated controls. The effect was observed 1.5 h after the first dose and was maintained for 24 h. After 5 days of dosing, the redns. in N-terminal telopeptides (NTx) and C-terminal telopeptides (CTx) of type I collagen were 61% and 67%, resp. A decrease in serum osteocalcin of 22% was also observed These data show that inhibition of cathepsin K results in a significant reduction of bone resorption in vivo and provide further evidence that this may be a viable approach to the treatment of postmenopausal osteoporosis.

IT 281217-45-6, SB 357114
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cathepsin K inhibitor leads to inhibition of bone resorption)
RN 281217-45-6 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 25 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry.

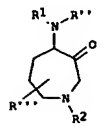


REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:713145 HCAPLUS
DOCUMENT NUMBER: 135:273219
TITLE: Preparation of C1-6 alkyl-4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Cummings, Maxwell D.; Marquis, Robert W., Jr.; Ru, Yu; Thompson, Scott K.; Veber, Daniel F.; Yamashita, Dennis S.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070232	A1	20010927	WO 2001-US7094	20010307
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2404206	AA	20010927	CA 2001-2404206	20010307
EP 1307203	A1	20030507	EP 2001-916412	20010307
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001009356	A	20030603	BR 2001-9356	20010307
JP 2003527429	T2	20030916	JP 2001-568430	20010307
NZ 520588	A	20040625	NZ 2001-520588	20010307
BG 106962	A	20030331	BG 2002-106962	20020729
ZA 2002007478	A	20031008	ZA 2002-7478	20020918
NO 2002004528	A	20021119	NO 2002-4528	20020920
US 2004044201	A1	20040304	US 2002-239343	20020920
PRIORITY APPLN. INFO.:			US 2000-191000P P	20000321
			US 2000-206341P P	20000523
			US 2000-211759P P	20000614
			US 2000-217445P P	20000710
			WO 2001-US7094 W	20010307

OTHER SOURCE(S): MARPAT 135:273219
GI



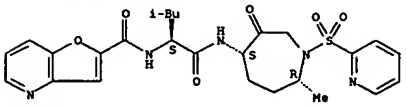
I

AB 4-Aminoazepan-3-one derivs. I [R1 is an acyl group R3CH2CO, R4NR'CRR3CO or R5-X-CHR3CO; R = H or RR3 = (CH2)n (n = 1-5); R2-R5 = H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, etc.; R', R'' = H, alkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl; X = CH2, S or O; R''' = alkyl; R3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring] or their pharmaceutically acceptable salts were prepd. as protease inhibitors for treating various diseases, including excessive bone loss or cartilage or matrix degrdn. Thus, 5-methoxybenzofuran-2-carboxylic acid [(S)-3-methyl-1-[(4S,6S)- (or 4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)azepan-4-ylcarbamoyl]butyl]amide was prepd. by a multistep procedure involving coupling of 4-amino-6-methyl-1-(pyridine-2-sulfonyl)azepan-3-ol (prepn. given) with Boc-Leu-OH and 5-methoxybenzofuran-2-carboxylic acid.

IT 362505-90-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of alkyl aminoazepanone derivs. as protease inhibitors)
RN 362505-90-6 HCAPLUS
CN Furo[3,2-b]pyridine-2-carboxamide, N-[(1S)-1-[[[(4S,7R)-hexahydro-7-methyl-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 26 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

Absolute stereochemistry.

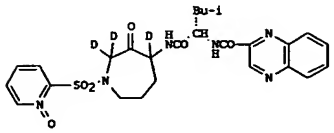


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359993 HCAPLUS
DOCUMENT NUMBER: 134:353552
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert Wells, Jr.; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034600	A1	20010517	WO 2000-US30757	20001108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1232154	A1	20020821	EP 2000-977089	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513972	T2	20030415	JP 2001-536547	20001108
US 6583137	B1	20030624	US 2002-129674	20020506
PRIORITY APPLN. INFO.:			US 1999-164560P P	19991110
			WO 2000-US30757 W	20001108

GI



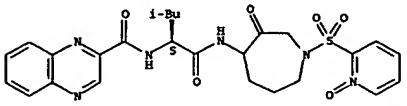
I

AB 2-Quinoxalinecarboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with 2-quinoxalinecarboxylic acid, hydroxyl group oxidation with pyridine-sulfur trioxide, and deuteration to afford I as a mixture of diastereomers which was separated by HPLC.

IT 339290-80-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

L4 ANSWER 27 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(prepn. of leucine aminoazepanone derivs. as protease inhibitors)
RN 339290-80-1 HCAPLUS
CN 2-Quinoxalinecarboxamide, N-[(1S)-1-[[[hexahydro-1-[(1-oxido-2-pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

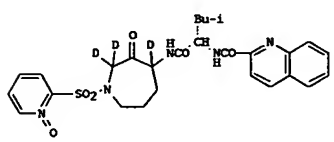


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 28 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359992 HCAPLUS
DOCUMENT NUMBER: 134:353551
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034599	A1	20010517	WO 2000-US30685	20001108
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1232155	A1	20020821	EP 2000-978423	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513971	T2	20030415	JP 2001-536546	20001108
US 6596715	B1	20030722	US 2002-129671	20020506
PRIORITY APPLN. INFO.:			US 1999-164634P P	19991110
			WO 2000-US30685 W	20001108

GI



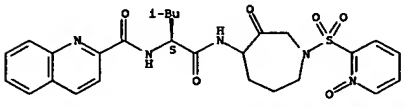
I

AB 2-Quinolinecarboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with 2-quinolinecarboxylic acid, hydroxyl group oxidation with pyridine-sulfur trioxide, and deuteration to afford I as a mixture of diastereomers which was separated by HPLC.

IT 339286-06-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of leucine aminoazepanone derivs. as protease inhibitors)
RN 339286-06-5 HCAPLUS
CN 2-Quinolinecarboxamide, N-[(1S)-1-[[[hexahydro-1-[(1-oxido-2-pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-

L4 ANSWER 28 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



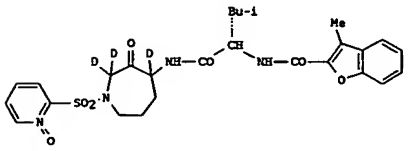
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 29 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359961 HCAPLUS
DOCUMENT NUMBER: 134:353550
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034566	A2	20010517	WO 2000-US30682	20001108
WO 2001034566	A3	20030731		
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
AU 2001014747	A5	20010606	AU 2001-14747	20001108
EP 1351930	A2	20031015	EP 2000-977056	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003533432	T2	20031111	JP 2001-536515	20001108

PRIORITY APPLN. INFO.: US 1999-164561P P 19991110
WO 2000-US30682 W 20001108

GI



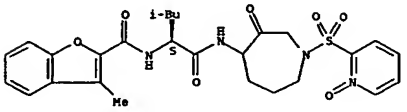
AB 3-Methylbenzofuran-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with 3-methylbenzofuran-2-carboxylic acid, hydroxyl group oxidation with pyridine-sulfur trioxide, and deuteration to afford I as a mixture of diastereomers which was separated by HPLC.

IT 339269-37-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

L4 ANSWER 29 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of leucine aminoazepanone derivs. as protease inhibitors)

RN 339269-37-3 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[hexahydro-1-[(1-oxido-2-pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-3-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

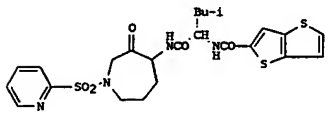


L4 ANSWER 30 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359960 HCAPLUS
DOCUMENT NUMBER: 134:353549
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Ru, Yu; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034565	A2	20010517	WO 2000-US30633	20001108
WO 2001034565	A3	20011004		
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1235577	A2	20020904	EP 2000-975608	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513956	T2	20030415	JP 2001-536514	20001108

PRIORITY APPLN. INFO.: US 1999-164511P P 19991110
WO 2000-US30633 W 20001108

GI



I

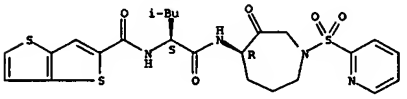
AB Thieno[3,2-b]thiophene-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride, Boc-deprotection, acylation with thieno[3,2-b]thiophene-2-carboxylic acid, and hydroxyl group oxidation with pyridine-sulfur trioxide to afford I as a mixture of diastereomers which was separated by HPLC. I showed Ki = 0.09 nM and
pit assay = 50 nM in cathepsin K inhibition studies.

IT 281215-75-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of leucine aminoazepanone derivs. as protease inhibitors)

RN 281215-75-6 HCAPLUS
CN Thieno[3,2-b]thiophene-2-carboxamide, N-[(1S)-1-[[[(4R)-hexahydro-3-oxo-1-

L4 ANSWER 30 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

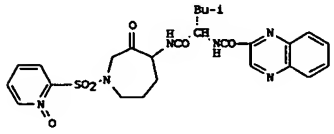
Absolute stereochemistry.



L4 ANSWER 31 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359809 HCAPLUS
DOCUMENT NUMBER: 134:353548
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Ru, Yu; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034160	A1	20010517	WO 2000-US30758	20001108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1229915	A1	20020814	EP 2000-978442	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513928	T2	20030415	JP 2001-536158	20001108
PRIORITY APPLN. INFO.:			US 1999-164562P	P 19991110
			WO 2000-US30758	W 20001108

GI



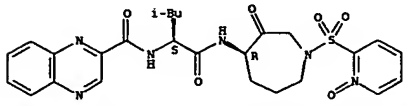
I

AB 2-Quinoxalinecarboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with 2-quinoxalinecarboxylic acid, and hydroxyl group oxidation with pyridine-sulfur trioxide to afford I as a mixture of diastereomers which was separated by HPLC. I showed Ki = 1.3 nM and pit assay ca. 100 nM in cathepsin K inhibition studies.

IT 281215-47-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

L4 ANSWER 31 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of leucine aminoazepanone derivs. as protease inhibitors)
RN 281215-47-2 HCAPLUS
CN 2-Quinoxalinecarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-1-[(1-oxido-2-pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

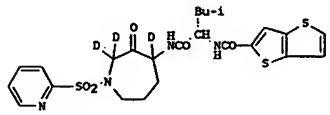


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 32 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359808 HCAPLUS
DOCUMENT NUMBER: 134:353547
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert Wells, Jr.; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034159	A1	20010517	WO 2000-US30704	20001108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1231922	A1	20020821	EP 2000-977066	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513927	T2	20030415	JP 2001-536157	20001108
PRIORITY APPLN. INFO.:			US 1999-164801P	P 19991110
			WO 2000-US30704	W 20001108

GI

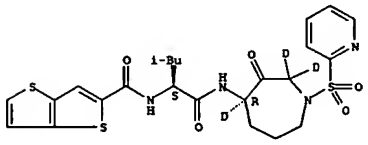


I

AB Thieno[3,2-b]thiophene-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride, Boc-deprotection, acylation with thieno[3,2-b]thiophene-2-carboxylic acid, hydroxyl group oxidation with pyridine-sulfur trioxide, and deuteration to afford I as a mixture of diastereomers which was separated by HPLC.

IT 339195-31-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of leucine aminoazepanone derivs. as protease inhibitors)
RN 339195-31-2 HCAPLUS
CN Thieno[3,2-b]thiophene-2-carboxamide, N-[(1S)-1-[[[(4R)-hexahydro-2,4-d2-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl-2-d]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 32 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry.

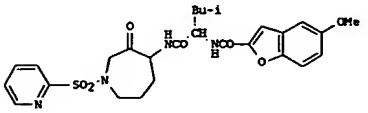


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 33 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359807 HCAPLUS
DOCUMENT NUMBER: 134:353546
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Ru, Yu; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034158	A1	20010517	WO 2000-US30703	20001108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1231921	A1	20020821	EP 2000-977065	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513926	T2	20030415	JP 2001-536156	20001108
PRIORITY APPLN. INFO.:			US 1999-164576P	P 19991110
			WO 2000-US30703	W 20001108

GI



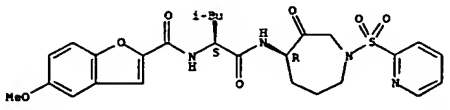
I

AB 5-Methoxybenzofuran-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride, Boc-deprotection, acylation with 5-methoxybenzofuran-2-carboxylic acid, and hydroxyl group oxidation with pyridine-sulfur trioxide to afford I as a mixture of diastereomers which was separated by HPLC. I showed Ki = 0.4 nM and pit assay = 75 nM in cathepsin K inhibition studies.

IT 281215-11-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

L4 ANSWER 33 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(prepn. of leucine aminoazepanone derivs. as protease inhibitors)
RN 281215-11-0 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-5-methoxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

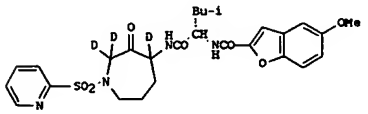


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 34 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359806 HCAPLUS
DOCUMENT NUMBER: 134:353545
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert Wells, Jr.; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034157	A1	20010517	WO 2000-US30702	20001108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1231923	A1	20020821	EP 2000-983690	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513925	T2	20030415	JP 2001-536155	20001108
PRIORITY APPLN. INFO.:			US 1999-164577P	P 19991110
			WO 2000-US30702	W 20001108

GI

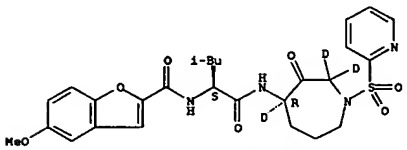


I

AB 5-Methoxybenzofuran-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride, Boc-deprotection, acylation with 5-methoxybenzofuran-2-carboxylic acid, hydroxyl group oxidation with pyridine-sulfur trioxide, and deuteration to afford I as a mixture of diastereomers which was separated by HPLC.

IT 339183-13-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of leucine aminoazepanone derivs. as protease inhibitors)
RN 339183-13-0 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-2,4-d2-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl-2-d]amino]carbonyl]-3-methylbutyl]-5-methoxy- (9CI) (CA INDEX NAME)

L4 ANSWER 34 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry.

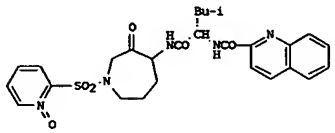


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 35 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359805 HCAPLUS
DOCUMENT NUMBER: 134:353544
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Ru, Yu; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034156	A1	20010517	WO 2000-US30684	20001108
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1229914	A1	20020814	EP 2000-977057	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513924	T2	20030415	JP 2001-536154	20001108
PRIORITY APPLN. INFO.:			US 1999-164578P P	19991110
			WO 2000-US30684 W	20001108

GI



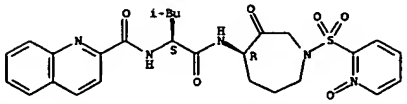
I

AB 2-Quinolinecarboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with 2-quinolinecarboxylic acid, and hydroxyl group oxidation with pyridine-sulfur trioxide to afford I as a mixture of diastereomers which was separated by HPLC. I showed Ki = 0.41 nM and pit assay = 300 nM in cathepsin K inhibition studies.

IT 281215-48-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

L4 ANSWER 35 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of leucine aminoazepanone derivs. as protease inhibitors)
RN 281215-48-3 HCAPLUS
CN 2-Quinolinecarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-1-[(1-oxido-2-pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

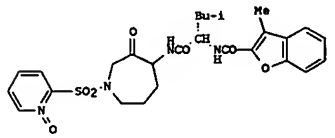


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 36 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359804 HCAPLUS
DOCUMENT NUMBER: 134:353543
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Ru, Yu; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034155	A1	20010517	WO 2000-US30681	20001108
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1233771	A1	20020828	EP 2000-977055	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513923	T2	20030415	JP 2001-536153	20001108
PRIORITY APPLN. INFO.:			US 1999-164800P P	19991110
			WO 2000-US30681 W	20001108

GI



I

AB 3-Methylbenzofuran-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with 3-methylbenzofuran-2-carboxylic acid, and hydroxyl group oxidation with pyridine-sulfur trioxide to afford I as a mixture of diastereomers which was separated by HPLC. I showed Ki = 0.11 nM and pit assay = 40 nM in cathepsin K inhibition studies.

IT 281215-58-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of leucine aminoazepanone derivs. as protease inhibitors)
RN 281215-58-5 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-1-[(1-oxido-2-

L4 ANSWER 36 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-3-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

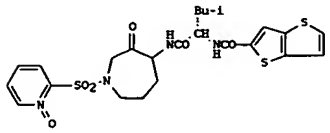
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 37 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359803 HCAPLUS
DOCUMENT NUMBER: 134:353542
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Ru, Yu; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034154	A1	20010517	WO 2000-US30634	20001108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1229912	A1	20020814	EP 2000-975609	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513922	T2	20030415	JP 2001-536152	20001108

PRIORITY APPLN. INFO.: US 1999-164559P P 19991110
WO 2000-US30634 W 20001108

GI



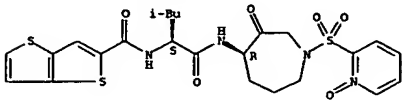
I

AB Thieno[3,2-b]thiophene-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with thieno[3,2-b]thiophene-2-carboxylic acid, and hydroxyl group oxidation with pyridine-sulfur trioxide to afford I as a mixture of diastereomers which was separated by HPLC. I showed Ki = 0.14 nM and pit assay = 45 nM in cathepsin K inhibition studies.

IT 281215-46-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

L4 ANSWER 37 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
(prepn. of leucine aminoazepanone derivs. as protease inhibitors)
RN 281215-46-1 HCAPLUS
CN Thieno[3,2-b]thiophene-2-carboxamide, N-[(1S)-1-[[[(4R)-hexahydro-1-[(1-oxido-2-pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



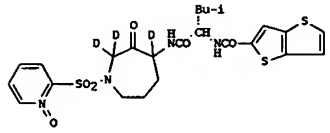
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 38 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:359802 HCAPLUS
DOCUMENT NUMBER: 134:353541
TITLE: Preparation of leucine 4-aminoazepan-3-one derivatives as protease inhibitors
INVENTOR(S): Marquis, Robert Wells, Jr.; Veber, Daniel Frank
PATENT ASSIGNEE(S): SmithKline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001034153	A1	20010517	WO 2000-US30632	20001108
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1229911	A1	20020814	EP 2000-975607	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003513921	T2	20030415	JP 2001-536151	20001108

PRIORITY APPLN. INFO.: US 1999-164515P P 19991110
WO 2000-US30632 W 20001108

GI



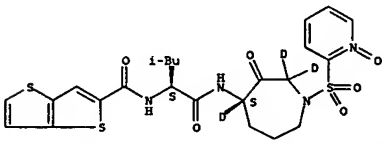
I

AB Thieno[3,2-b]thiophene-2-carboxylic acid amide I or a pharmaceutically acceptable salt, hydrate or solvate was prepared as an inhibitor of cysteine proteases, particularly cathepsin K, and is useful in the treatment of diseases in which inhibition of bone loss or of cartilage degradation is a factor. Thus, 4-amino-3-hydroxyazepane-1-carboxylic acid benzyl ester (preparation given) underwent sequential coupling with Boc-Leu-OH, catalytic hydrogenolysis, sulfonylation with 2-pyridinesulfonyl chloride N-oxide, Boc-deprotection, acylation with thieno[3,2-b]thiophene-2-carboxylic acid, hydroxyl group oxidation with pyridine-sulfur trioxide, and deuteration to afford I as a mixture of diastereomers which was separated by HPLC.

IT 339075-63-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of leucine aminoazepanone derivs. as protease inhibitors)

RN 339075-63-7 HCAPLUS
CN Thieno[3,2-b]thiophene-2-carboxamide, N-[(1S)-1-[[[(4S)-hexahydro-2,4-d2-1-[(1-oxido-2-pyridinyl)sulfonyl]-3-oxo-1H-azepin-4-yl-2-d]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

L4 ANSWER 38 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
Absolute stereochemistry.



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

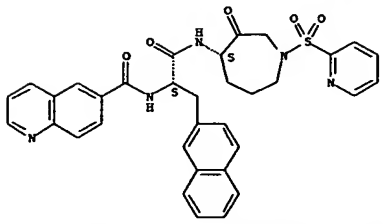
L4 ANSWER 39 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:318582 HCAPLUS
DOCUMENT NUMBER: 135:120165
TITLE: Potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro
AUTHOR(S): James, Ian E.; Marquis, Robert W.; Blake, Simon M.; Ewang, Shing Mei; Gress, Catherine J.; Ru, Yu; Zembryki, Denise; Yamashita, Dennis S.; McQueney, Michael S.; Tomaszek, Thaddeus A.; Oh, Hye-Ja; Gowen, Maxine; Veber, Daniel F.; Lark, Michael W.
CORPORATE SOURCE: Departments of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Journal of Biological Chemistry (2001), 276(15), 11507-11511
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cathepsins K and L are related cysteine proteases that have been proposed to play important roles in osteoclast-mediated bone resorption. To further examine the putative role of cathepsin L in bone resorption, we have evaluated selective and potent inhibitors of human cathepsin L and cathepsin K in an in vitro assay of human osteoclastic resorption and an in situ assay of osteoclast cathepsin activity. The potent selective cathepsin L inhibitors (Ki = 0.0099, 0.034, and 0.27 nM) were inactive in both the in situ cytochem. assay (IC50 > 1 μM) and the osteoclast-mediated bone resorption assay (IC50 > 300 nM). Conversely, the cathepsin K selective inhibitor was potently active in both the cytochem. (IC50 = 63 nM) and resorption (IC50 = 71 nM) assays. A recently reported dipeptide aldehyde with activity against cathepsins L (Ki = 0.052 nM) and K (Ki = 1.57 nM) was also active in both assays (IC50 = 110 and 115 nM, resp.) These data confirm that cathepsin K and not cathepsin L is the major protease responsible for human osteoclastic bone resorption.

IT 350796-38-2
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro)
RN 350796-38-2 HCAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

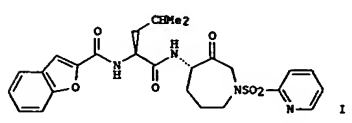
Absolute stereochemistry.

L4 ANSWER 39 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

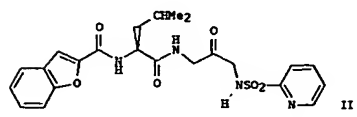


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 40 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:215566 HCAPLUS
DOCUMENT NUMBER: 135:5780
TITLE: Azepanone-Based Inhibitors of Human and Rat Cathepsin K
AUTHOR(S): Marquis, Robert W.; Ru, Yu; LoCastro, Steven M.; Zeng, Jin; Yamashita, Dennis S.; Oh, Hye-Ja; Erhard, Karl F.; Davis, Larry D.; Tomaszek, Thaddeus A.; Tew, David; Salyers, Kevin; Proksch, Joel; Ward, Keith; Smith, Brian; Levy, Mark; Cummings, Maxwell D.; Haltiwanger, R. Curtis; Trescher, Gudrun; Wang, Bing; Hemling, Mark E.; Quinn, Chad J.; Cheng, H-Y.; Lin, Fan; Smith, Ward W.; Janson, Cheryl A.; Zhao, Baoguang; McQueney, Michael S.; D'Alessio, Karla; Lee, Chao-Pin; Marzulli, Antonia; Dodds, Robert A.; Blake, Simon; Ewang, Shing-Mei; James, Ian E.; Gress, Catherine J.; Bradley, Brian R.; Lark, Michael W.; Gowen, Maxine; Veber, Daniel F.
CORPORATE SOURCE: Departments of Medicinal Chemistry Mechanistic Enzymology Drug Metabolism and Pharmacokinetics Physical and Structural Chemistry Structural Biology Protein Biochemistry Life-Cycle Management and Drug Delivery Systems and Bone and Cartilage Biology, GlaxoSmithKline, King of Prussia, PA, 19406, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(9), 1380-1395
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



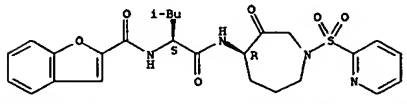
II

AB The synthesis, in vitro activities, and pharmacokinetics of a series of azepanone-based inhibitors of the cysteine protease cathepsin K (EC 3.4.22.38) are described. These compds. show improved configurational stability of the C-4 diastereomeric center relative to the previously published five- and six-membered ring ketone-based inhibitor series. Studies in this series have led to the identification of azepanone I, a potent, selective inhibitor of human cathepsin K (Ki = 0.16 nM) as well as the acyclic analog II, a potent inhibitor of both human (Ki = 0.0048 nM) and rat (Ki,app = 4.8 nM) cathepsin K. Small-mol. X-ray crystallog. anal. of I established the C-4 S stereochem. as being crit. for potent inhibition and that unbound I adopted the expected equatorial conformation for the C-4 substituent. Mol. modeling studies predicted the higher energy axial orientation at C-4 of I when bound within the active site of cathepsin K, a feature subsequently confirmed by X-ray crystallog. Pharmacokinetic studies in the rat show I to be 42% orally bioavailable. Comparison of the transport of the cyclic and acyclic analogs through CaCo-2 cells suggests that oral bioavailability of the acyclic derivs. is limited by a P-glycoprotein-mediated efflux mechanism. It is concluded that the introduction of a conformational constraint has served the dual purpose of increasing inhibitor potency by locking in a bioactive conformation as well as locking out available conformations which may serve as substrates for enzyme systems that limit oral bioavailability.

L4 ANSWER 40 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

IT 281214-75-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent)
(preparation of benzofurylcarbonylleucylazepinone cathepsin K inhibitors)
RN 281214-75-3 HCAPLUS
CN 2-Benzofurancarboxamide, N-[(1S)-1-[[[(4R)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



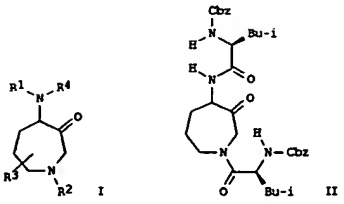
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 41 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:456887 HCAPLUS
DOCUMENT NUMBER: 133:89444
TITLE: Preparation of 4-amino-azepan-3-one protease inhibitors
INVENTOR(S): Marquis, Robert Wells, Jr.; Ru, Yu; Veber, Daniel Frank; Cummings, Maxwell David; Thompson, Scott Kevin; Yamashita, Dennis
PATENT ASSIGNEE(S): Smithkline Beecham Corp., USA
SOURCE: PCT Int. Appl., 273 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038687	A1	20000706	WO 1999-US30730	19991221
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356671	AA	20000706	CA 1999-2356671	19991221
BR 9916488	A	20011009	BR 1999-16488	19991221
EP 1158986	A1	20011205	EP 1999-963112	19991221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200101869	T2	20020121	TR 2001-200101869	19991221
JP 2002533397	T2	20021008	JP 2000-590640	19991221
AU 768565	B2	20031218	AU 2000-19411	19991221
NZ 511710	A	20031219	NZ 1999-511710	19991221
EP 1384713	A1	20040128	EP 2003-76211	19991221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY				
ZA 2001004208	A	20020523	ZA 2001-4208	20010523
US 2003144175	A1	20030731	US 2001-881334	20010614
NO 2001003124	A	20010622	NO 2001-3124	20010622
NO 318910	B1	20050523		
US 2002147188	A1	20021010	US 2002-74940	20020213
US 2003044399	A1	20030306	US 2002-74639	20020213
US 2003225061	A1	20031204	US 2003-404142	20030401
US 2004002487	A1	20040101	US 2003-404716	20030401
US 2005256104	A1	20051117	US 2005-152745	20050614
PRIORITY APPLN. INFO.:			US 1998-113636P	P 19981223
			US 1999-164581P	P 19991110
			EP 1999-963112	A3 19991221
			WO 1999-US30730	W 19991221
			US 2000-593845	B2 20000614
			US 2000-653815	A1 20000901
			US 2001-881334	A1 20010614
			US 2002-74940	A1 20020213
			US 2003-404716	B1 20030401

OTHER SOURCE(S): MARPAT 133:89444

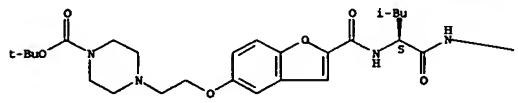
L4 ANSWER 41 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)
GI



AB The title compds. [I; R1 = COCR13NR11R12, COCR13XR15, COCH2R13; R2 = H, alkyl, cycloalkylalkyl, etc.; R3 = H, alkyl, cycloalkylalkyl, etc.; R4 = H, alkyl, arylalkyl, etc.; R11 = H, alkyl, arylalkyl, etc.; R12 = H, alkyl, cycloalkyl, etc.; R13 = H, alkyl, alkenyl, etc.; R15 = H, alkyl, alkenyl, etc.] which inhibit proteases (no data), including cathepsin K, and are useful for treating diseases of excessive bone loss or cartilage or matrix degradation including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease, were prepared E.g., a multi-step synthesis of compound II was given. Compds. I are effective at 0.4-400 mg/kg/day.
IT 281214-88-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of 4-amino-azepan-3-one protease inhibitors)
RN 281214-88-8 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[2-[[2-[[[(1S)-1-[[[hexahydro-2-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]carbonyl]-3-methylbutyl]amino]carbonyl]-5-benzofuranyl]oxy]ethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

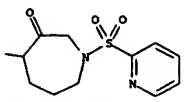
Absolute stereochemistry.

PAGE 1-A



L4 ANSWER 41 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)

PAGE 1-B



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

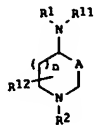
L4 ANSWER 42 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:112238 HCAPLUS
DOCUMENT NUMBER: 128:192935
TITLE: Preparation of heterocyclic peptide derivatives as cysteine protease inhibitors
INVENTOR(S): Marquis, Robert W., Jr.; Veber, Daniel F.; Ru, Yu; Lo, Castro Stephen
PATENT ASSIGNEE(S): Smithkline Beecham Corp., USA; Marquis, Robert W. Jr.; Veber, Daniel F.; Ru, Yu; Lo Castro, Stephen
SOURCE: PCT Int. Appl., 176 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9805336	A1	19980212	WO 1997-US13875	19970807
W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AP 865	A	20000817	AP 1997-1054	19970806
W: BW, GM, GH, KE, LS, MW, SD, SZ, UG, ZM, ZW				
CA 2262668	AA	19980212	CA 1997-2262668	19970807
AU 9739726	A1	19980225	AU 1997-39726	19970807
AU 721853	B2	20000713		
ZA 9707032	A	19980804	ZA 1997-7032	19970807
EP 936912	A1	19990825	EP 1997-937146	19970807
EP 936912	B1	20040211		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
CN 1232399	A	19991020	CN 1997-198532	19970807
NZ 333987	A	20000929	NZ 1997-333987	19970807
BR 9711044	A	20001024	BR 1997-11044	19970807
JP 2000516920	T2	20001219	JP 1998-508213	19970807
IL 128378	A1	20031031	IL 1997-128378	19970807
AT 259352	E	20040215	AT 1997-937146	19970807
PT 936912	T	20040630	PT 1997-937146	19970807
ES 2213831	T3	20040901	ES 1997-937146	19970807
TW 542825	B	20030721	TW 1997-86111564	19970922
BG 64412	B1	20050131	BG 1999-103144	19990203
NO 9900548	A	19990407	NO 1999-548	19990205
NO 317182	B1	20040906		
KR 2000029863	A	20000525	KR 1999-701027	19990206
HK 1022096	A1	20041105	HK 2000-101085	20000223
US 2002128476	A1	20020912	US 2001-836586	20010417
US 2004180927	A1	20040916	US 2004-789063	20040227
PRIORITY APPLN. INFO.:			US 1996-23742P	P 19960808
			US 1997-46867P	P 19970508
			WO 1997-US13875	W 19970807
			US 1999-230791	B1 19990208
			US 2000-658256	B1 20000908
			US 2001-836586	A1 20010417

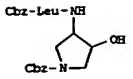
OTHER SOURCE(S): MARPAT 128:192935
GI

Pregrant Pub.

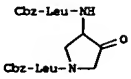
L4 ANSWER 42 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



I



II



III

AB Title heterocycles I [A = CO, CH(OH); R11, R12, R9, R6 = = H, C1-6 alkyl, C3-6 cycloalkyl-C0-6 alkyl, Ar-C0-6 alkyl, Het-C0-6 alkyl; R1 = R4R10NCHR3Z, ARCHR9CO, 4-(Ph-Y)C6H4CO, dibenzofuran-2-sulfonyl; R2 = any group R11, R5CO, R5CS, R5SO2, R5O2C, R5R10NCO, R5R10NCS, adamantyl-CO, R6R7NCHR3-Z; R3 = H, C2-6 alkenyl, C2-6 alkynyl, Het, Ar, C1-6 alkyl (un)substituted by OR10, SR10, NR102, R10NCO2R5, CO2R10, CO2NR102, NC:NHNH2, Het, Ar; R4, R7 = any group R11, R5CO, R5CS, R5SO2, R5O2C, R5R10NCO, R5R10NCS, R10HNCHR10CO, R5O2CNR10CHR10CO; R5 = C3-6 cycloalkyl-C0-6 alkyl, Ar-C0-6 alkyl, Het-C0-6 alkyl, Ar-C0-6 alkoxy, Het-C0-6 alkoxy, C1-6 alkyl (un)substituted by OR10, SR10, NR102, R10NCO2R5, CO2R10, CO2NR102, NC:NHNH2, Het, Ar; NR6R7 = pyrrolidino, piperidino, morpholino; R10 = H, C1-6 alkyl, Ar-C0-6 alkyl, Het-C0-6 alkyl; Y = bond, O; Z = CO, CH2; n = 0-2; Ar = aryl, Het = heterocyclyl] or a pharmaceutically acceptable salt thereof, are inhibitors of cysteine proteases, particularly cathepsin K, and are useful in the treatment of diseases in which inhibition of bone loss is a factor. Thus, coupling of 1-tert-butoxycarbonyl-trans-3-amino-4-hydroxypyrrolidine (preparation given) with Cbz-Leu-OH (Cbz = PhCH2O2C), followed by deprotection with HCl in EtOAc and further coupling with Cbz-Leu-OH gave trans-pyrrolidinol II. Jones oxidation of II gave desired title compound III.

IT 203501-66-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

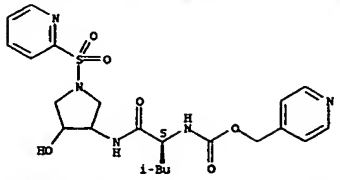
(preparation of heterocyclic peptide derivs. as cysteine protease inhibitors)

RN 203501-66-0 HCAPLUS

CN Carbamic acid, [1-[[[4-hydroxy-1-(2-pyridinylsulfonyl)-3-pyrrolidinyl]amino]carbonyl]-3-methylbutyl]-, 4-pyridinylmethyl ester, [3(S)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 42 OF 42 HCAPLUS COPYRIGHT 2005 ACS on STN (Continued)



Elected species

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT